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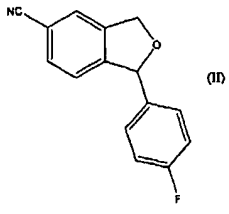
(54) Title: METHOD FOR THE PREPARATION OF CITALOPRAM



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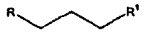

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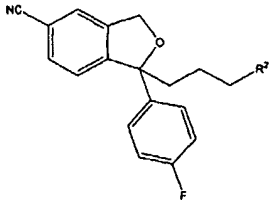


(IV)

(57) Abstract: The invention relates to a method for the preparation of citalopram comprising reaction of a compound of formula (II) with a compound having the formula (III) wherein R is halogen or -O-SO_2-X, wherein X is alkyl, alkenyl, alkynyl or optionally alkyl substituted aryl or aralkyl, and R^1 is dimethylamino, halogen, -O-SO_2-X wherein X is as defined above, provided that R is not halogen when R^1 is dimethylamino; and if R^1 is dimethylamino followed by isolation of citalopram base or a pharmaceutically acceptable acid addition salt thereof, and if R^1 is halogen or -O-SO_2-X, wherein X is as defined above, followed by conversion of the resulting compound of formula wherein R^2 is halogen or a group of formula -O-SO_2-X wherein X is as defined above to citalopram, followed by isolation of citalopram base or a pharmaceutically acceptable acid addition salt thereof.

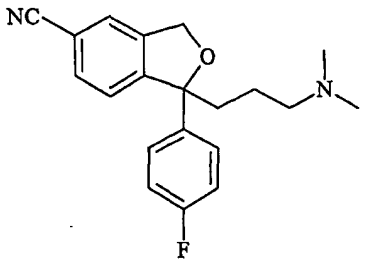
WO 01/51478 A1

Method for the Preparation of Citalopram

The present invention relates to a method for the preparation of the well-known antidepressant drug citalopram, 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile.

Background of the Invention

Citalopram is a well-known antidepressant drug that has now been on the market for some years and has the following structure:



(I)

It is a selective, centrally acting serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitor, accordingly having antidepressant activities. The antidepressant activity of the compound has been reported in several publications, eg. J. Hyttel. *Prog. Neuro-Psychopharmacol. & Biol. Psychiat.* **1982**, *6*, 277-295 and A. Gravem *Acta Psychiatr. Scand.* **1987**, *75*, 478-486. The compound has further been disclosed to show effects in the treatment of dementia and cerebrovascular disorders, EP-A-474580.

Citalopram was first disclosed in DE 2,657,013, corresponding to US 4,136,193. This patent publication describes the preparation of citalopram by one method and outlines a further method which may be used for preparing citalopram.

According to the process described, the corresponding 1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile is reacted with 3-(N,N-dimethylamino)propyl-chloride in the presence of methylsulfinylmethide as condensing agent. The starting material was prepared from the corresponding 5-bromo derivative by reaction with cuprous cyanide.

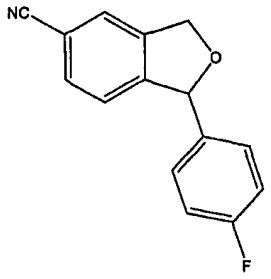
International patent application No. WO 98/019511 discloses a process for the manufacture of citalopram wherein a (4-(cyano, alkyloxycarbonyl or alkylaminocarbonyl)-2-hydroxymethylphenyl-(4-fluorophenyl)methanol compound is subjected to ring closure. The resulting 5-(alkyloxycarbonyl or alkylaminocarbony)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran is converted converted to the corresponding 5-cyano derivative and the 5-cyano derivative is then alkylated with a (3-dimethylamino)propylhalogenide in order to obtain citalopram.

It has now, surprisingly, been found that citalopram may be manufactured by a novel favourable process.

The alkylation process according to the invention is particularly advantageous because the formation of by-products by polymerisation of the alkylating agent is avoided whereby a reduction in the amount of alkylating reagent to be used is made possible. The process of the invention also provides high yields.

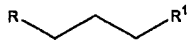
Summary of the invention

Accordingly, the present invention relates to a method for the preparation of citalopram comprising reaction of a compound of formula



(II)

with a compound having the formula

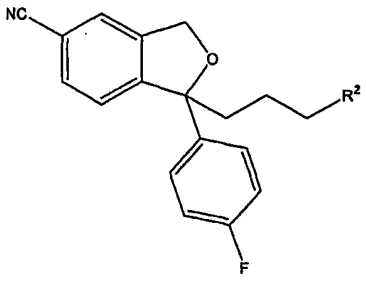


(III)

wherein R is halogen or -O-SO_2-X wherein X is alkyl, alkenyl, alkynyl or optionally alkyl substituted aryl or aralkyl and R^1 is dimethylamino, halogen or -O-SO_2-X wherein X is as defined above, provided that R is not halogen when R^1 is dimethylamino;

and if R^1 is dimethylamino followed by isolation of citalopram base or a pharmaceutically acceptable acid addition salt thereof,

and if R^1 is halogen or -O-SO_2-X wherein X is as defined above, followed by conversion of the resulting compound of formula



(IV)

wherein R^2 is halogen or a group of formula -O-SO_2-X, wherein X is as defined above, to citalopram, followed by isolation of citalopram base or a pharmaceutically acceptable acid addition salt thereof.

Thus in one embodiment, the present invention relates to a method where a compound of formula (II) is reacted with a compound of formula (III) wherein R is -O-SO_2-X wherein X is as defined above and R^1 is dimethylamino resulting in the direct formation of citalopram.

In a second embodiment, the present invention relates to a method where a compound of formula (II) is reacted with a compound of formula (III) wherein R and R^1 are independently selected from halogen and -O-SO_2-X. The resulting compound of formula (IV) wherein R^2 is halogen or a group of formula -O-SO_2-X, where X is as defined above, is then converted to citalopram by reaction with

a) dimethylamin or a metal salt thereof,
b) methylamin followed by reductive amination, or
c) an azide followed by reduction to form the corresponding amino compound and thereafter methylation or reductive amination.

In another aspect, the present invention provides the novel intermediates of the general formula (IV).

In yet another aspect, the present invention relates to an antidepressant pharmaceutical composition comprising citalopram manufactured by the process of the invention.

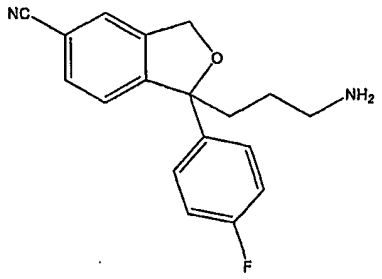
The alkylation step where the compound of formula (II) is reacted with a compound of formula (III) is suitably carried out by treatment of the compound of formula (II) with a base such as for example LDA (lithium diisopropylamine), LiHMDS (lithium hexamethyldisilazane), NaH, NaHMDS (sodium hexamethyldisilazane), or metalalkoxides such as NaOMe, KOMe, LiOMe, NaO*tert*Bu, KO*tert*Bu and LiO*tert*Bu in an aprotic organic solvent such as THF (tetrahydrofurane), DMF (dimethylformamide), NMP (N-methylpyrrolidon), ethers such as diethylether, or dioxalane, toluene,

benzene or alkanes and mixtures thereof. The anion formed is then reacted with a compound of formula (III) whereby a group of formula $-CH_2-CH_2-CH_2-R^2$ or a group of formula $-CH_2-CH_2-CH_2-N(CH_3)_2$ is introduced into position 1 of the isobenzofuranyl ring system.

The compound of formula (IV) is then reacted with dimethylamin or a metal salt thereof, such as $M^+,^-N(CH_3)_2$ wherein M^+ is Li^+ or Na^+. The reaction is suitably carried out in an aprotic organic solvent such as THF (tetrahydrofurane), DMF (dimethylformamide), NMP (N-methyl pyrrolidon), ethers such as diethylether, or dioxalane, toluene, benzene, or alkanes and mixtures thereof. The compound of formula (IV) may also be converted to citalopram by reaction with dimethylammonium chloride.

The reaction conditions, solvents, etc. used for the reactions described above are conventional conditions for such reactions and may easily be determined by a person skilled in the art.

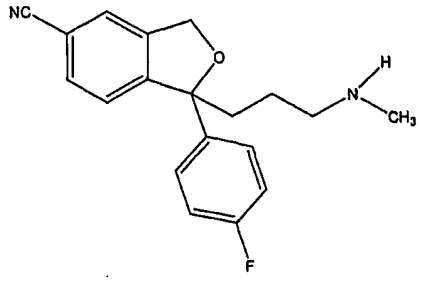
Alternatively, the compound of formula (IV) is reacted with an azide, such as sodium azide, followed by reduction, using e.g. Pd/C as a catalyst, to form the corresponding amine of formula



(V)

and thereafter methylation or reductive amination to form citalopram.

The compound of formula (IV) may also be converted to citalopram by reaction with methylamine to form a compound of formula



(VI)

followed by methylation or reductive amination to form citalopram.

The amino groups in the compounds of formula (V) and (VI) may be methylated with methylating agents such as MeI and Me_2SO_4 wherein Me is methyl. The methylation is carried out using conventional procedures for carrying out such reactions.

Methyl groups may also be introduced into the compounds of formula (V) or (VI) by reductive amination. According to this procedure, the compounds of formula (V) or (VI) are reacted with compounds such as formaldehyde, paraformaldehyde or trioxan in presence of a reducing agent such as $NaBH_4$ or $NaBH_3CN$. The reductive amination is carried out using conventional procedures for carrying out such reactions.

The starting material of formula (II) may be prepared as described in US patent No. 4,136,193 or as described in WO 98/019511.

The compounds of formula (III) are known or may be prepared from known compounds using conventional methods.

Citalopram is on the market as an antidepressant drug in the form of the racemate. However, in the near future, the active S-enantiomer of citalopram is also going to be introduced to the market.

S-citalopram may be prepared by separation of the optically active isomers by chromatography.

Throughout the specification and claims, the term alkyl refers to a branched or unbranched alkyl group having from one to six carbon atoms inclusive, such as methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-2-propyl, 2,2-dimethyl-1-ethyl and 2-methyl-1-propyl.

Similarly, alkenyl and alkynyl, respectively, designate such groups having from two to six carbon atoms, including one double bond or triple bond respectively, such as ethenyl, propenyl, butenyl, ethynyl, propynyl and butynyl.

The term aryl refers to a mono- or bicyclic carbocyclic aromatic group, such as phenyl and naphthyl, in particular phenyl.

The term aralkyl refers to aryl-alkyl, wherein aryl and alkyl is as defined above.

Optionally, alkyl substituted aryl and aralkyl refers to aryl and aralkyl groups, which may optionally be substituted with one or more alkyl groups.

Halogen means chloro, bromo or iodo.

The compound of general Formula I may be used as the free base, in particular as citalopram base in crystalline form, or as a pharmaceutically acceptable acid addition salt thereof. As acid addition salts, such salts formed with organic or inorganic acids may be used. Exemplary of such organic salts are those with maleic, fumaric, benzoic, ascorbic, succinic, oxalic, bismethylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzene sulfonic and theophylline acetic acids, as well as the 8-halotheophyllines, for example 8-bromotheophylline. Exemplary of such inorganic salts are those with hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric and nitric acids.

The acid addition salts of the compounds may be prepared by methods known in the art. The base is reacted with either the calculated amount of acid in a water miscible solvent, such as acetone or ethanol, with subsequent isolation of the salt by concentration and cooling, or with an excess of the acid in a water immiscible solvent, such as ethylether, ethylacetate or dichloromethane, with the salt separating spontaneously.

The pharmaceutical compositions of the invention may be administered in any suitable way and in any suitable form, for example orally in the form of tablets, capsules, powders or syrups, or parenterally in the form of usual sterile solutions for injection.

The pharmaceutical formulations of the invention may be prepared by conventional methods in the art. For example, tablets may be prepared by mixing the active ingredient with ordinary adjuvants and/or diluents and subsequently compressing the mixture in a conventional tabletting machine. Examples of adjuvants or diluents comprise: Corn starch, potato starch, talcum, magnesium stearate, gelatine, lactose, gums, and the like. Any other adjuvant or additive, colourings, aroma, preservatives etc. may be used provided that they are compatible with the active ingredients.

Solutions for injections may be prepared by dissolving the active ingredient and possible additives in a part of the solvent for injection, preferably sterile water, adjusting the solution to the desired volume, sterilising the solution and filling it in suitable ampoules or vials. Any suitable additive conventionally used in the art may be added, such as tonicity agents, preservatives, antioxidants, etc.

The invention is further illustrated by the following examples.

Example 1

A solution of 1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (4.8 g, 0.02 mol) in THF(50 ml) was added dropwise to a solution of LDA (butyl lithium 1.6 M (15 mL) , diisopropylamine (2.6 g)) at –30° C under an atmosphere of nitrogen. After stirring at - 30° C for 10 minutes a solution of the alkyl halide/sulphonate (0.02 mol) in THF (25 mL) was added dropwise and allowed to warm to room temperature and stirred for a further 60 minutes. The reaction was then quenched with ice, extracted with toluene (3 x 50 mL), washed with water (50 mL) and concentrated under reduced pressure. The residue was purified by chromatography on silica gel using mixtures of n-heptane/EtOAc as the eluent. The resulting anion is the reacted with a compound of formula (III).

Example 2

Preparation of 1-[3-(*N,N*-dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran-carbonitrile (Citalopram, Oxalate):

To a solution of 1-(4-fluorophenyl)-1-[(3-*p*-toluenesulfonyloxy)propyl]-1,3-dihydro-5-isobenzo-furancarbonitrile (0.20 g, 0.4 mmol) in DMF (10 mL) was added triethylamine (1.4 mL, 7.0 mmol) and dimethylammonium chloride (0.41g, 5.0 mmol). The reaction mixture was stirred at 70 °C overnight, then cooled to room temperature, poured into ice/H_2O and extracted with Et_2O (3 × 30 mL). The organic extracts were washed with H_2O and brine, and evaporated. The residue was purified by silica gel chromatography (heptane, EtOAc, triethylamine 1:3:4%) and crystallised from acetone as the oxalate salt (0.12 g, 70%). DSC (open chamber), T_{onset} = 158.96, T_{peak} = 162.14.^{1}H NMR (DMSO-d_6) δ 1.42 (1H, m); 1.51 (1H, m); 2.22 (2H, t, J = 8.0 Hz); 2.62 (6H, s); 2.95 (2H, t, J = 8.0 Hz); 5.15 (1H, d, J = 14.0 Hz); 5.23 (1H, d, J = 14.0 Hz); 7.18 (2H, t, J = 9.0 Hz); 7.59 (2H, dd, J = 5.0 and 8.0 Hz); 7.74 (1H, d, J = 7.5 Hz); 7.79 (1H, d, J = 7.0 Hz); 7.80 (1H, br s). ^{13}C NMR (DMSO-d_6) δ 19.3; 37.0; 42.3; 56.7; 71.2; 90.3; 110.7; 115.2; 115.3; 118.8; 123.2; 125.8; 127.0; 132.1; 139.9; 140.0; 148.161.4; 164.3. Anal. ($C_{20}H_{21}N_2O$, $C_2H_2O_4$) calcd. C: 63.76; H: 5.59; N: 6.76. Found C: 63.50; H: 5.78; N: 6.63.

Example 3

Preparation of 1-[3-(*N,N*-dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile (Citalopram, Oxalate):

Dimethylamine (18 mL, 100 mmol, 33% in ethanol) was added to a solution of 1-(4-fluorophenyl)-1-[(3-methanesulfonyloxy)propyl]-1,3-dihydro-5-isobenzofurancarbonitrile (1.0 g, 2.7 mmol) in ethanol (10 mL) and THF (20 mL). The resulting mixture was stirred at room temperature for 1 h and at 60 °C for 3 h. After cooling, the reaction mixture was evaporated. 1 M NaOH (70 mL) was added to the residue and extracted with Et_2O (100 mL). The organic extract was washed with brine, dried and evaporated. The residue was filtered through silica gel (EtOAc, heptane, triethylamine 75:25:1) and crystallised from acetone as the oxalate salt (0.72 g, 65%). DSC (open chamber), T_{onset} = 158.56, T_{peak} = 161.59. The NMR-spectra were identical with those obtained from citalopram. oxalate prepared in example 2. Anal. ($C_{20}H_{21}N_2O$, $C_2H_2O_4$) calcd. C: 63.76; H: 5.59; N: 6.76. Found C: 63.57; H: 5.51; N: 6.77.

Example 4

Preparation of 1-(3-Azidopropyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile:

Sodium azide (5.5 g, 80.5 mmol) was added to a solution of 1-(4-fluorophenyl)-1-[(3-methanesulfonyloxy)propyl]-1,3-dihydro-5-isobenzofurancarbonitrile (4.0 g, 10.6 mmol) in DMF (100 mL). The resulting mixture was stirred at 40 °C for 3 h, and then refluxed for 2 h. After cooling the reaction mixture was poured into H_2O and extracted with Et_2O (4 × 200 mL). The organic extracts were washed with H_2O and brine, dried and evaporated to give the crude product as a brown oil (1.3 g, 45%). ^{1}H NMR (DMSO- d_6) δ 1.40 (2H, m); 2.22 (2H, m); 3.30 (2H, t, J = 6.6 Hz); 5.10 (1H, d, J = 13.7 Hz); 5.21 (1H, d, J = 13.7 Hz); 7.18 (2H, t, J = 8.5 Hz); 7.59 (2H, dd, J = 5.2 and 8.5 Hz); 7.78 (3H, s + d, J = 8.1 Hz).

Preparation of 1-(3-Aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile:

A mixture of 1-(3-azidopropyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbo-nitrile (1.3 g, 4.4 mmol) and palladium on carbon (0.6 g, 5%) in ethanol (50 mL) was hydrogenated for 2 h. The mixture was filtered through Celite and evaporated to give the crude product as a brown oil (0.8 g, 66%). ^{1}H NMR (DMSO- d_6) δ 1.11 (1H, m); 1.22 (1H, m); 2.12 (2H, m); 2.48 (2H, t, J = 7.1 Hz);

5.15 (1H, d, J = 13.7 Hz); 5.19 (1H, d, J = 13.7 Hz); 7.15(2H, t, J = 8.9 Hz); 7.58 (2H, dd, J = 5.2 and 8.5 Hz); 7.72 (1H, d, J = 8.4 Hz); 7.78 (2H, s + d, J = 8.1 Hz).

Preparation of 1-[3-(*N,N*-Dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile, (Citalopram, Oxalate):

Sodium cyanoborohydride (0.34 g, 5.4 mmol) was added to a mixture of 1-(3-Aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile (0.80 g, 2.7 mmol) and formaldehyde (0.44 mL, 5.4 mmol, 37% in H_2O) in methanol (10 mL). The resulting mixture was stirred at room temperature for 3 h, then was added more sodium cyanoborohydride (0.17 g, 2.7 mmol) and formaldehyde (0.22 mL, 2.7 mmol). After stirring at room temperature for 1 h, the mixture was quenched with H_20 and extracted with Et_20. The organic extracts were dried and evaporated. Silica gel chromatography (EtOAc, heptane, triethylamine 75:25:1) of the residue gave the crude product, which was isolated as the oxalate salt from acetone (0.31 g, 0.8 mmol, 30 %). The NMR-spectra were identical with those obtained from citalopram oxalate prepared in example 2. Anal. ($C_{20}H_{21}N_2O$, $C_2H_2O_4$, ¼ H_20) calcd. C: 63.06; H: 5.67; N: 6.69. Found C: 63.28; H: 5.64; N: 6.67.

Example 5

Preparation of 1-(4-fluorophenyl)-1-[3-(*N*-methylamino)propyl]-1,3-dihydro-5-isobenzofurancarbonitrile, Oxalate Salt:

The compound was prepared from methylamine (60 mL, 120 mmol, 2 M solution in THF) using the method described in example 3. Yield: 760 mg, 36%. ^{1}H NMR (DMSO- d_6) δ 1.40 (1H, m); 1.41 (1H, m); 2.25 (2H, t); 2.47 (3H, s); 2.83 (2H, t, J = 8.0 Hz); 5.15 (1H, d, J = 13.2 Hz); 5.21 (1H, d, J = 13.2 Hz); 7.18 (2H, t, J = 9.0 Hz); 7.59 (2H, dd, J = 5.6 and 7.5 Hz); 7.73 (1H, d, J = 8.1 Hz); 7.81 (3H, d + s, J = 8.1 Hz).

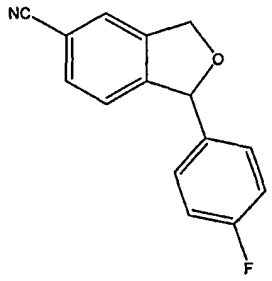
Preparation 1-[3-(*N,N*-Dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile, (Citalopram, Oxalate):

A solution of 1-[3-(*N*-methyl-ammonium)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile (0.70 g, 2.24 mmol) and formaldehyde (0.5 mL, 6.7 mmol, 37% aqueous solution) in 98% formic acid (5 mL) was refluxed for 4 h. After cooling, 4 M HCl (2 mL) was added and the resulting mixture was evaporated. 1 M NaOH (50 mL) was added to the residue and extracted with Et_2O (3 × 100 mL). The organic extract was washed with brine, dried and evaporated. The oxalate salt was

isolated from acetone (0.22 g, 30%). DSC (open chamber), T_{onset} = 157.73, T_{peak} = 160.80. The NMR-spectra were identical with those obtained from citalopram. oxalate prepared in example 2. Anal. ($C_{20}H_{21}N_2O$, $C_2H_2O_4$, ¼ H_20) calcd. C: 63.06; H: 5.67; N: 6.69. Found C: 63.24; H: 5.65; N: 6.62.

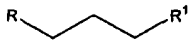
CLAIMS

1. A method for the preparation of citalopram comprising reaction of a compound of formula II



(II)

with a compound having the formula

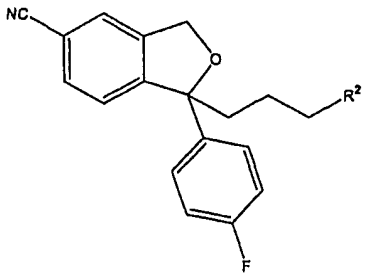


(III)

wherein R is halogen or -O-SO_2-X wherein X is alkyl, alkenyl, alkynyl or optionally alkyl substituted aryl or aralkyl and R^1 is dimethylamino, halogen, -O-SO_2-X wherein X is as defined above, provided that R is not halogen when R^1 is dimethylamino;

and if R^1 is dimethylamino followed by isolation of citalopram base or a pharmaceutically acceptable acid addition salt thereof,

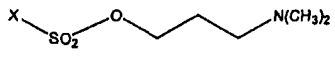
and if R^1 is halogen or -O-SO_2-X wherein X is as defined above, followed by conversion of the resulting compound of formula



(IV)

wherein R^2 is halogen or a group of formula -O-SO_2-X wherein X is as defined above to citalopram, followed by isolation of citalopram base or a pharmaceutically acceptable acid addition salt thereof.

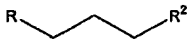
2. A method for the preparation of citalopram according to claim 1 comprising reacting the compound of formula II with a sulphonyl ester having the formula



(IIIa)

wherein X is as defined in claim 1 followed by isolation of citalopram base or a pharmaceutically acceptable acid addition salt thereof.

3. The method for the preparation of citalopram according to claim 1 comprising reaction of a compound of formula (II) with a compound having the formula



(IIIb)

wherein R and R^2 is as defined in claim 1, followed by reaction of the resulting compound of formula (IV) with

a) dimethylamin or a metal salt thereof,
b) methylamin followed by reductive amination, or
c) an azide followed by reduction to form the corresponding amino compound and thereafter methylation or reductive amination,

to form citalopram.

4. The method according to claims 1-3 wherein the reaction of a compound of formula (II) with a compound of formula (III) is carried out in presence of a base selected from LDA (lithium-diisopropylamine), LiHMDS (hexamethyldisilasan lithium), NaH, NaHMDS (hexamethyldisilasan-sodium) and metalalkoxides such as NaOMe, KOMe, LiOMe, NaO*tert*Bu, KO*tert*Bu and LiO*tert*B.

5. An antidepressant pharmaceutical composition comprising citalopram manufactured by the process of any of claims 1-4.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 01/00140

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 307/87
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9819511 A2 (H. LUNDBECK A/S), 14 May 1998 (14.05.98)	1-4
X	--	5
A	Eur. J. Med. Chem. - Chimica Therapeutica, Volume 12, No 3, 1977, Allan J. Bigler et al, "Quantitative structure-activity relationships in a series of selective 5-HT uptake inhibitors", page 289 - page 295, Method B	1-4
X	--	5

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 June 2001	18 -06- 2001
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson/EÖ Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

Information on patent family members

30/04/01

International application No.
PCT/DK 01/00140

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9819511 A2	14/05/98	AU 5116798 A	29/05/98
		BG 104487 A	31/01/01
		BR 9714924 A	26/09/00
		DE 1032566 T	15/03/01
		EP 1032566 A	06/09/00
		ES 2149141 T	01/11/00
		NO 20002267 A	06/07/00
		PL 340774 A	26/02/01
		ZA 9810059 A	05/05/99